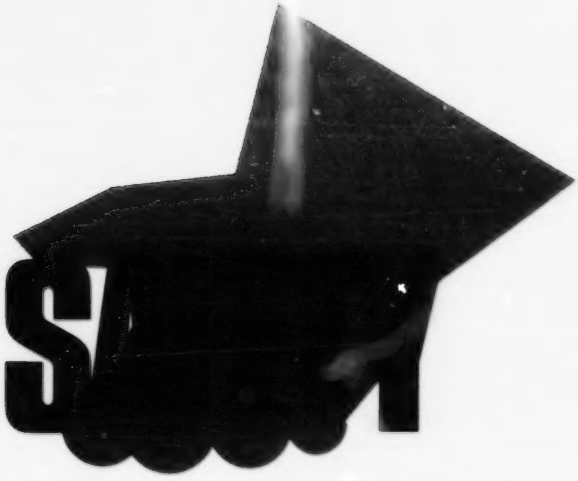
Minister

Human Resources, Labour and Employment

Occupational Health and Safety Branch



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Antineoplastic Drugs

Introduction

Antineoplastic (anti-new growth; anti-cancer) drugs are toxic to cells and may pose an occupational health risk to health care workers. In therapeutic doses these agents produce toxic side effects due to their poor selectivity between target (cancer cells) and normal cells. There is ample evidence that many of these drugs induce neoplasms and leukemias, cause testicular and ovarian dysfunction including permanent sterility, produce cumulative chromosome damage and are associated with organ damage in cancer patients receiving long-term therapy. Animal studies confirm the potential of these agents to induce malignancy and to cause chromosomal damage and reproductive abnormalities. Appendix 1 lists carcinogenic and carcinosuspect antineoplastic drugs.

Reasons for Concern

In recent years, there has been a considerable increase in concern over the potential occupational hazards associated with the handling of injectable antineoplastic drugs. Various studies have shown:

- detectable levels of antineoplastic drugs in the air of hospital units with no hoods;
- detectable amounts of various drugs in the urine of health care workers handling them;
- the ability of the drugs to cause increased frequency of chromosome damage among exposed workers;
- some reported acute effects among exposed workers which include skin, eyes and mucous membrane irritations, allergic reactions upon contact with the skin as well as subjective symptoms including nausea, headache and dizziness;
- that there is a higher incidence of spontaneous abortions and a higher risk of delivering malformed babies among some groups of exposed female workers.

There is, however, no adequate evidence at the present time that repeated occupational exposures to small amounts of antineoplastic drugs over a long period of time causes cancer.

Not all antineoplastic drugs are carcinogenic. In particular, antimetabolites such as methotrexate (amethopterin), cytarabine (cytosar) and 5-fluorouracil (5-FU) have not caused cancer in animal studies or in humans receiving therapeutic treatments, despite their uses in large numbers of patients over many years. The alkylating agents (in particular nitrogen mustards, ethylenimine derivates and nitrosoureas) on the other hand, have been shown repeatedly to be carcinogenic in laboratory systems and in cancer patients. Some evidence inferring potential for male or female reproductive toxicity exist, however, for most members of antineoplastic agents. Therefore, precautions should be followed to limit occupational exposure to all of them.

Sources of Exposure

The main routes of exposure of workers are through the inhalation of drug dust or aerosol, absorption through the skin and ingestion through contact with contaminated food or cigarettes. The aerosol is generated during the preparation or the administration of the drug, e.g. as a

result of breaking open of ampules, withdrawal of needles from drug vials, drug transfers using syringes, or the expulsion of air from a drug-filled syringe. Such aerosol can result in exposing not only the worker immediately involved, but also other people in the surrounding areas.

Responsibilities For Controlling Exposure

The Occupational Health and Safety Act and regulations require every employer to ensure, insofar as is reasonably practicable,[1] the health and safety at work of all workers. Section 72 of *The Occupational Health and Safety Regulations* requires the employer to take all practicable[2] steps to prevent the exposure of workers to any harmful chemical substances to any extent likely to be harmful to their health and to take all reasonably practicable steps to minimize the danger to workers from those substances. Such steps include provision of sufficient and suitable ventilation (whether general or local exhaust), provision of personal protective equipment and personal washing facilities, ensuring adequate labelling, provision of a system for handling spills and emergencies and ensuring that workers are provided with adequate instruction regarding proper and safe handling of the harmful chemical. Workers are required to co-operate with the employer in the discharge of the employer's responsibilities and to use the safeguards and safety equipment provided pursuant to the regulations.

Guidelines for Controlling Exposures

The following guidelines are the Branch's interpretation of *The Occupational Health and Safety Act* and regulations as they pertain to handling antineoplastic drugs in hospitals. As such, they will enable hospitals to comply with the requirements of the law and hence, the provision of an adequate level of control for the health risk associated with these drugs.

1) Where it is reasonably practicable, the employer should provide, maintain and ensure proper use of a suitable mechanical ventilation system for the removal of antineoplastic drug dust or aerosol from the breathing zone of workers preparing the drugs and to prevent the dust or aerosol from dispersing or accumulating into other work areas.

   a) The Branch considers it reasonably practicable to provide a mechanical ventilation system at any hospital where antineoplastic drugs are prepared on a daily basis. Class II or class III biological safety cabinets are suitable and provide appropriate protection.

   b) At present class II biological safety cabinets Types A, B1, B2 or B3, are considered appropriate. This is because there is no evidence that partial recirculation of HEPA filtered downflow air increases the risk of worker exposure. Neither is there evidence that recirculation of HEPA filtered exhausted air presents a significant risk of contamination. Preference should, however, be given to a Type B cabinet (exhausted to the outdoor) and in particular, to a Type B2 (downflow air is not recirculated from the cabinet exhaust air).

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[1] "reasonably practicable" means practicable unless the person on whom a duty is placed can show that there is a gross disproportion between the benefit of the duty and the cost, in time, trouble and money, of the measures to secure the duty

[2] "practicable" means physically possible in the light of current knowledge and invention

c) The biological safety cabinet should be examined for its performance and certified by a competent technician at least annually and every time the cabinet is moved.

d) The exhaust blower on the biological safety cabinet should be operated continuously - even when not in use.

e) The cabinet should be cleaned daily with 70% alcohol and decontaminated weekly or whenever spills occur. Decontamination should consist of surface cleaning with an alkaline detergent followed by thorough rinsing. Personal protective equipment as described in guideline #3 should be used while decontaminating the cabinet.

f) The duct work attached to the cabinet should be labelled as to hazardous content.

2) Where it is not reasonably practicable to provide a safety cabinet, a centralized area for the preparation of antineoplastic drugs should be designated.

a) The area should be a quiet, uncluttered work area and although ventilated, not be subject to direct air flow from a ventilation system, fan or air conditioning unit. The area should be clearly posted with a sign identifying it as an antineoplastic drug preparation area.

b) Workers preparing antineoplastic drugs at the designated area should be provided with and use an air-purifying respirator[1] equipped with a high efficiency filter carrying the National Institute for Occupational Safety and Health (NIOSH) approval number TC-21C (the filter is commonly described as for protection against dusts, fumes and mists having a time-weighted average less than 0.05 mg/m^3 and radionuclides).

c) Workers should be trained in using the respirator to ensure proper fit and to prevent contamination of the inner surface of the respirator. The respirator should be cleaned and inspected after each day's use. The cartridge should be replaced according to manufacturer's recommendations. When not in use, the respirator should be stored in a dust-proof sanitary location.

3) Personal protective equipment should be provided for and used by workers preparing or administering the drugs. These should include disposable surgical latex gloves and a protective gown made of low permeability fabric with a closed front, long sleeves and closed cuffs. A pair of splash goggles should be made available for use in any situation where there is a risk of eye splashes and for cleaning the spills.

a) Gloves should be routinely changed approximately every hour or immediately if they are torn or punctured. Double gloving is recommended for cleaning up spills.

b) Potentially contaminated gowns or gloves should not be worn outside the work area.

c) Hands must be washed before and after gloving.

d) If an accidental spill or splash occurs, contaminated clothing should be removed immediately and contaminated skin or eyes should be flushed immediately with copious amounts of running water to effectively cleanse the area.

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[1] The respirator is available at any safety equipment outlet.

4) Suitable preparation, administration and waste disposal equipment should be made available to and used by the workers. These include:

   a) disposable, absorbent, plastic backed sheeting to cover the work area and potential leakage areas;

   b) disposable needles and hydrophobic filter units (eg. Millex-FG) to vent reconstituted vials to reduce internal pressure and potential for spillage or liquid spraying when a needle is withdrawn from the vial septum (one manufacturer suggests using 0.2µm filter units);

   c) all syringes and intravenous sets with Luer-lock fittings;

   d) disposal collection container such as a plastic or metal tray lined with sterile gauze to collect excess solution;

   e) a closable, puncture-resistant container for disposal of contaminated sharp/breakable materials;

   f) labelled, sealable or wiretie plastic bags of sufficient thickness (4 mil thick polyethylene or 2 mil polypropylene) for the collection of waste including used gloves, paper liners, used disposable gowns, unused pills, powder residues and containers, and used gauze and alcohol wipes; and

   g) spill cleaning material including absorbent gauze pads, spill control pillows, a small scoop to collect glass fragments, a 5% sodium thiosulfate solution and a 5% sodium bicarbonate solution to inactive nitrogen mustard types of antineoplastic drugs.

5) The employer should provide information, instruction, training and supervision to workers exposed to antineoplastic drugs.

   a) Pre-job training should be given to all personnel involved in the mixing and/or administration of antineoplastic drugs. This should include familiarization with known risks associated with these drugs. The training should be continually assessed and reinforced.

   b) Written work procedures or specific instructions should be formulated or otherwise obtained[1] and be made available to all personnel involved in the mixing and/or administration of the drugs. These should include:

      i) proper techniques for preparation and administration of the drugs including means of reducing aerosolization;
      ii) waste collection, handling and disposal;
      iii) spill clean-up and personnel decontamination procedures;

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[1] There are several printed procedures available, eg. Saskatchewan Cancer Foundation Guidelines, the U.S. Occupational Health and Safety Administration Guidelines, Canadian Society of Hospital Pharmacists Guidelines, the American Pharmaceutical Society Guidelines, etc. Any of these documents should be obtained and adapted to the hospital.

iv) procedure for dealing with blood, vomitus or excreta and linen or laundry contaminated therewith from patients who have received antineoplastic drugs in the last 48 hours;

v) storage and transport of antineoplastic drugs including procedures to safely deal with damaged packages;

vi) instructions to observe an appropriate personal hygiene standard including prohibition of eating, drinking, smoking, application of cosmetics or storing food in or near the preparation area; and

vii) familiarization of housekeeping, laundry and janitorial staff with the potential hazards of handling laundry, excreta, etc., contaminated with antineoplastic drugs and safe work procedures when handling same.

6) Pregnancy

On the basis of the available evidence, it seems reasonable to assume that if appropriate procedures are followed and proper equipment and protection are provided, reproductive hazards will be reduced. However, every employer should, as far as possible, transfer a pregnant or breast-feeding worker, if she so wishes, to comparable duties that do not involve handling antineoplastic drugs. A policy covering male or female personnel who are actively trying to conceive a child should also be established.

Appendix 1

GROUP 1 - Drugs which are carcinogenic* (sufficient human evidence of carcinogenesis)

Azathioprine (Amuran)
Busulfan (Myleran)
Certain combined chemotherapy for lymphomas: eg. procarbazine, vincristine, prednisone and nitrogen mustard
Chlorambucil (Leukeran)
Cyclophosphamide (Cytoxan, Procytox)
Melphalan (Alkeran)

GROUP 2A - Drugs which are probably carcinogenic to humans* (generally, limited human evidence, but sufficient animal evidence)

Bischloroethyl nitrosourea or carmustine (BiCNU)
1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea or lomustine (CeeNU)
Cisplatin (Platinol)
Doxorubicin (Adriamycin)
Nitrogen mustard (Mustargen)
Procarbazine (Natulan)
Triethylene thiophosphoramide (Thiotepa)

GROUP 2B - Drugs which are possibly carcinogenic to humans* (generally, limited human evidence, but absence of animal evidence)

Bleomycin sulfate (Blenoxane)
Dacarbazine (DTIC)
Mitomycin (Mutamycin)
Streptozocine (Zanosar)

Drugs with evidence of carcinogenicity which, at present, are not used clinically in Canada.

Chlornaphazine (GROUP 1)
1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea or Methyl-CCNU (GROUP 1)
Treosulphan (GROUP 1)
Aminouracil mustard or Uracil mustard (GROUP 2B)
Nitrogen mustard, n-oxide (GROUP 2B)

*Source:

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7, 1987.

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